REMARKS

Claims 1-20 were filed in the original case. Claims 1-20 were cancelled and claims 21-41 were added in a previous amendment. Claims 21-41 were cancelled and claims 42-73 were added in a previous amendment. Claims 42-73 are cancelled in the present amendment. These cancellations are made without acquiescing to the Examiner's rejections, but are made to further prosecution and Applicant's business interests. Applicant reserves the right to prosecute claims 42-73 (or similar claims) in the future. Claims 74-105 are added with the present amendment. Therefore claims 74-105 are currently pending.

In the Office Action dated July 1, 2003, the Examiner has withdrawn rejections from the previous Office Action. However, the Examiner has maintained one rejection and added a second rejection. The currently pending rejections are:

1) Claims 42-73 stand rejected under 35 U.S.C. §103(a).

2) Claim 55 stands rejected under 35 U.S.C. §103(a).

Claims 42-73 are cancelled herein, rendering these rejections moot. Applicant believes that the Examiner has failed to establish a *prima facie* case for obviousness of the pending claims. Therefore claims 74-105 should be passed into allowance

Applicants have filed Information Disclosure Statements on 10/11/00 and 4/25/01 and request that the Examiner initial all associated Form 1449s.

I. CLAIMS 74-105 ARE NON-OBVIOUS

A. The Examiner's Rejection is Defective as a Matter of Law

In the Office Action of 07/01/2003 the Examiner has rejected cancelled claims 42-73 as allegedly being obvious in view of a number of references (previously cited), with the still further addition of Hoon *et al.* (US pat. 6,057,105) (hereinafter referred to as Hoon) in the present rejection:

"Claims 42-73 are rejected under 35 U.S.C. §103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No 10, page 3698-3703, 1996), and further in view of Hoon et al. (US Pat. 6,057,105)."
(Office Action 07/01/2003, page 4).

In the Office Action of 07/01/2003 the Examiner perseverates in failing to meet the Patent and Trademark Office's legal responsibility to first establish a *prima facie* case of obviousness supported by objective evidence **prior to** any necessity by the Applicant to rebut the Examiner's position. The Examiner has never provided objective evidence demonstrating a motivation to combine or modify the cited references. Lacking objective evidence, the Examiner fails to apply the proper legal standard of obviousness in substituting an idiosyncratic, novel and improper "clearly recognized benefit" standard. The addition of Hoon to the Examiner's antecedent and bulky combination of references fails to remedy these defects. Because the Examiner cannot evade the Patent and Trademark Office's obligation to provide objective evidence of obviousness as a first step, and because the Examiner cannot create new law in the absence of objective evidence, the rejections must be withdrawn. Applicants need not provide any evidence to rebut the Examiner's position for the rejection to be overturned. Yet Applicant has provided evidence. In previous Office Actions, the Examiner has addressed this evidence (arguing that it is insufficient) as though doing so were sufficient to maintain the rejection. However, the Examiner has **never** responded, as required by law, to Applicants assertion that the Examiner has not made a *prima facie* showing in the first place.

B. The Examiner Must First Establish *Prima Facie* Obviousness and Hasn't

In the Office Action of 07/01/2003 the Examiner repetitively asserts unsupported and conclusory allegations regarding the obviousness of the present invention. For example:

"Regardless of whether the test is viewed as not cost effective for broad application for all patients, it remains obvious to sample individuals before surgery for know (sic) mutations which affect surgical outcomes." (Page 13).

And:

"Finally, the ordinary artisan would have been motivated to have assayed for genetic markers prior to surgery to enable the detection of markers which are negatively associated with surgical conditions so that the conditions may be avoided." (Page 13).

And:

"The ordinary artisan would have been motivated to have screened individuals to provide individualized surgery to determine the genetic composition of the individuals to provide individualized diagnosis." (Page 10).

These representative quotations in the Office Action of 07/01/2003, and their ilk, are remarkable for their utter lack of supporting objective evidence sustaining the Examiner's speculations with regard, for example, to what an ordinary artisan would or would not have recognized, or been motivated to do. As a first step in making the determination of *prima facie* obviousness, it is compulsory for the Patent and Trademark Office and the Examiner to provide such evidence, and there is none. To the contrary, the Examiner's many-layered combinations are guided only in hindsight recognition that the presently claimed invention is useful. No evidence has been supplied. The entire basis of the rejection relies on the Examiner's unsupported beliefs and opinions. The rejections cannot stand.

For example, the Examiner has failed to point to objective evidence of any teaching, suggestion or motivation to make the Examiner's impermissible combinations. As detailed infra. (I.D.), the Examiner's supernumerary addition of Hoon fails to render the claimed invention obvious. Despite the added combination of Hoon, none of the references cited by the Examiner alone, in combination, or in combinations of combinations, teach or suggest detecting two or more genetic markers in two or more genes clinically associated with two or more conditions for

use in the perioperative interval. None of the references, alone or in combination, teach or suggest generation of a genomic profile for use in selecting a perioperative course of action.

Under 35 U.S.C. §103(a) the Examiner cannot avoid establishing the *prima facie* case of obviousness case supported by objective evidence. As obligated by law, the Examiner's burden must first be met with evidence of obviousness in the form of a reference, affidavit, declaration, or other **evidence** besides the Examiner's guesses, speculations or unsupported personal opinions. This burden exists to prevent the Examiner from making an unsupported *prima facie* case so as to prevent Applicant from having to present evidence to rebut a fiction—a proposition that may not be possible. For example, in the present case, the prior art is silent on a motivation to combine references as suggested by the Examiner. The Examiner has presented a rejection based only on speculation and personal belief about such a motivation. Applicant is left with no concrete evidence to counter or to contradict. Had the Examiner presented a reference suggesting a motivation, Applicant would be able to respond to the context of the reference and address its weaknesses. Here, Applicant is left to address a phantom. Now that the phantom has been created, the Examiner is looking to Applicant to produce evidence from the prior art of the absence of the phantom. Of course this is impossible. The prior art will never have a statement that discusses reasons not to move in the direction of an invention that is **yet to be conceived**. This is the very reason why the Patent Office has the initial burden of demonstrating a *prima facie* case of obviousness supported with **objective evidence**. Only then can Applicant explain why the cited evidence does not stand for the proposition offered by the Examiner. In the absence of first meeting the Patent and Trademark Office's burden in putting forth evidence of obviousness, the Patent and Trademark Office cannot ask the Applicant for proof of non-obviousness.

Nevertheless, proof of non-obviousness is exactly what the Examiner improperly demands of the Applicant. For example, the Examiner argues:

> "The response has provided no technical reasons why the ordinary artisan **would *not* have been motivated** to have assayed for genetic mutations prior to surgery which are known to be associated with consequences during a surgical procedure." (Office Action 07/01/2003, Page 12). (Emphasis added).

And:

> "While it is clear that many in the medical field do not believe that routine genetic testing provides sufficient valuable information to warrant its cost, this does not imply that the art **has *not* conceived of** or thought about perioperative genetic testing." (Office Action 07/01/2003, page 15).

Contrary to the Examiner's misapprehensions, in the absence of objective evidence in support of the *prima facie* case of obviousness, it is **not** the Applicant's burden to provide "technical reasons why the ordinary artisan **would *not* have been motivated**" to make the claimed invention. Nor is it the Applicant's burden to prove that the art **had *not* thought of something**. The only way to meet the Examiner's novel legal standard would be if the invention were described in the prior art (it is not), and then if the same or a second reference said not to do it (none can exist). However, the Applicant is under no such burden, and case law specifically precludes the Patent and Trademark Office from engaging in this activity (see Section I.D.2. infra.). Rather than asking the Applicant for proof of non-obviousness, it is Examiner's initial responsibility to provide objective evidence of obviousness, for example, that the ordinary artisan was motivated to make the claimed invention, or that the art had taught or suggested the invention. The Examiner has failed in this duty in impermissibly shifting the evidentiary burden to the Applicant prior to establishing a *prima facie* case of obviousness.

As detailed in Section I.D.2. infra., the Courts require the Examiner to provide objective evidence of obviousness as a first step, which the Applicant may then refute. The allocation of the burden of proof as to obviousness is discussed in MPEP §2141 and §2142. The provision states "the examiner bears the initial burden of **factually supporting** any prima facie case of obviousness," and "if the examiner does not produce a prima facie case, the applicant is under no obligation to submit evidence of non-obviousness." (Emphasis added). Here, the Examiner has failed to provide objective evidence of obviousness in the first instance. Therefore the Applicant is under no legal duty to rebut a *prima facie* case. While under no obligation, and in order to further prosecution of the present case, the Applicant has provided ample, specific and objective evidence in the form of published references, peer reviews, a Declaration, and a Practice Advisory showing the Examiner's inability to fabricate a *prima facie* case of obviousness (see

I.E. infra.). This evidence documents that at the time the invention was made ordinary artisans did not, and do not, agree with the Examiner regarding the benefits of genetic testing before surgery. In the Office Action of 07/01/2003 the Examiner has mischaracterized and dismissed, but not contradicted, this evidence demonstrating that the Examiner's speculations are in error.

Because the Examiner's *prima facie* case lacks objective evidence of record supporting a conclusion of obviousness, the Examiner's rejection of cancelled claims 42-73, and improper efforts to shift the evidentiary burden to the Applicant, are procedurally defective under the MPEP and the law.

C. Lacking Evidence of Obviousness, the Examiner has Attempted to Create New Law

Because objective evidence in support of a *prima facie* case of obviousness is lacking (for example, there is no teaching, suggestion or motivation in the prior art to make the Examiner's combinations), the Examiner has improperly attempted to create a novel legal standard of obviousness. In the Office Action of 07/01/2003 the Examiner repetitively argues that the invention is obvious because its benefits are clear, that is, that the invention is so useful that an artisan of ordinary skill would have recognized or been motivated to make the invention. For example, the Examiner argues:

> "The ordinary artisan would have **clearly recognized the benefit** of testing an individual prior to surgery and subjection to anesthesia for known genetic markers associated with a condition which was triggered by anesthetics." (Office Action 07/01/2003, page 9).

> And:

> "The ordinary artisan would have been motivated to have screened individuals to provide individualized surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any known genes for known mutations which are associated with known conditions **for the expected benefit** of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure." (Office Action 07/01/2003, page 10).

And:

"The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The **benefit of screening** individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise." (Office Action 07/01/2003, page 10).

And:

"... the skilled artisan would be motivated to screen markers which were well known at the time of the art simultaneously or in tandem **for the benefits** of providing the most complete amount of information possible." (Office Action 07/01/2003, page 11).

And:

"While routine screening has not yet reached the point of being cost effective and highly efficient, the cited art still provides suggestion that with regard to RYR1, BchE, prothrombin, etc. genes, testing prior to surgery would be **certainly advantageous** since mortality and complications may be avoided." (Office Action 07/01/2003, page 15).

Applicant does not dispute the advantages and benefits of the present invention as originally disclosed by Applicant to the Patent ant Trademark Office, and presently acknowledged by the Examiner. But the Examiner's mere recitation of these benefits is insufficient evidence of the invention's obviousness. The benefits of the invention, no matter how clear-cut to the Examiner in hindsight, are no substitute for objective evidence, for example, regarding what an ordinary artisan would have recognized or been motivated to do. Hence, the Examiner's reiterations of the invention's benefits do not satisfy requirements for establishing the *prima facie* case of obviousness. Accordingly, the Examiner can point to no statute or case law supporting the proposition that an invention that is very

useful is therefore obvious. To the contrary, if the Examiner's standard were law, clearly recognized benefits would void all useful applications for obviousness.

Despite the benefits of the present invention, nowhere in the prior art of record has the Examiner identified a teaching, suggestion or motivation to detect two or more nucleic acid genetic markers in two or more genes associated with two or more conditions in a sample from a perioperative subject to generate a genomic profile for use in selecting a perioperative course of action. In an attempt to remedy this defect the Examiner adds Hoon to the pile of previously cited combinations, arguing:

> "In a particular example, Hoon demonstrates that number of masitive (?) markers was studied and that using four markers was **significantly better** than a single marker alone (col.21) **Therefore, it would have been prima facie obvious** to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics . . .". (Office Action 07/01/2003, page 8). (Emphasis added).

The Examiner's conclusory and impermissible "therefore" clause again reflects the Examiner's confusion regarding the proper obviousness standard in conflating significant benefits with obviousness. As well, Hoon lacks key elements of the present invention, provides no reasonable expectation of success, and does not teach, suggest or motivate combinations that the Examiner has selected guided only by the present invention (see I.D., infra). As detailed supra, it is a matter of law that to sustain the rejection the Examiner must put forth actual evidence. Instead the Examiner impermissibly substitutes the utility of the present invention for obviousness, concluding that because the invention is very useful, it is therefore obvious. The Examiner's arguments are conclusory, unsupported, and wrong.

The Examiner's actions in failing to establish a *prima facie* case of obviousness, in improper shifting of the evidentiary burden, in attempting to create and apply a novel legal standard of obviousness, and in reiteration of errors of both fact and well-settled matters of law are unacceptable and inequitable. The Examiner must provide evidence, or allow the claims.

D. Hoon Does Not Remedy the Defects of the Examiner's Rejection

In the preceding Office Action the Examiner has conceded:

"None of the cited references specifically discuss testing multiple known markers which are associated with different conditions, i.e. known genetic markers into a single assay for determining whether individuals are at risk during surgical procedures." (Office Action 10/18/2002, page 21).

To make up for this deficiency the Examiner cited Miller in a series of combinations with other references. In response, the Applicant pointed out to the Examiner that the claims recite testing two or more nucleic acid markers, in two or more genes, to generate a genomic profile for use in the perioperative interval, and that the Miller reference does not mention even one of these limitations, giving no instruction for genomic testing whatsoever, or of the particular criteria necessary to select the genomic markers to one of ordinary skill in the art. (Amendment and Response to Final Office Action Dated October 18, 2002, pages 9-10).

In the present Office Action of 07/01/2003 the Examiner concedes:

"Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "two or more known genetic variations." (Page 5.)

In the present Office Action of 07/01/2003 the Examiner attempts to remedy this defect with the still further combination of Hoon:

"Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays." (Office Action 07/01/2003, page 8)

However, the Examiner has erroneously mischaracterized and minimized the conceded defect. Absence of "two or more known genetic variation" is not the only defect of Miller combined with the Examiner's other references. Neither Miller or Hoon alone, or in combination, or in combination with the Examiner's other combinations provide detection of two or more nucleic acid genetic markers in **two or more genes** associated with **two or more conditions** to generate a **genomic profile** in a **sample from a perioperative subject** for use in selecting a **perioperative course of action**. Moreover, as detailed supra and infra, absence of "two or more known genetic variations" is not the only defect of the present rejection in many

other regards. Hence, Hoon fails to fill large and numerous gaps in the Examiner's attempt to establish a *prima facie* case of obviousness.

A *prima facie* case of obviousness requires the Examiner to cite to a reference which a) discloses all the elements of the claimed invention, b) suggests or motivates one of ordinary skill in the art to combine the claim elements to yield the claimed invention, and c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements negates a finding of a *prima facie* case and, without more, entitles the Applicants to allowance of the claims in issue. (MPEP) The Examiner argues that cancelled claim 55 and added claim 87, would have been obvious to one of ordinary skill in the art. To the contrary, the Examiner has failed to establish not one, but all three of the requirements for a *prima facie* case of obviousness, thus entitling Applicant to withdrawal of this rejection.

1. **The Combination of Hoon with Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No 10, page 3698-3703, 1996) <u>Does Not Teach All Elements of the Claims</u>.**

   The Hoon patent teaches:

   ". . . methods for the detection of melanoma **<u>or</u>** breast cancer cells in a biologic sample. The methods provide for the detection of melanoma **<u>or</u>** breast cancer cells in a biological sample by amplifying at least two nucleic acid markers from the sample, the nucleic acids being markers for melanoma **<u>or</u>** breast cancer cells."

   (Summary of the Invention, paragraph 1.) (Emphasis added.)

Under Hoon, breast cancer patients are tested for breast cancer alleles, or melanoma patients are tested for melanoma alleles, with one set of markers for one condition and another set of markers for another condition. In either case the markers are tissue and cancer specific.

Alone or in combination with the Examiner's other references, Hoon does not teach two or more nucleic acid markers in two or more genes for two or more conditions in the perioperative subject of the present claims. Hoon does not teach testing the same sample from the same perioperative subject for the two or more conditions.

As well, alone or in combination with the Examiner's other references, Hoon does not teach the genomic profile elements of the present claims, for example, **Claim 74** genomic profiles "for use in selecting a perioperative course of action", or **Claim 87** genomic profiles "for use in selecting a surgical procedure treatment course of action", or **Claim 94 and 101** genomic profiles "for use by a physician in determining a risk for complications during a surgical procedure", or **Claim 102** genomic profiles "consulted in selecting an appropriate anesthesia treatment for said subject."

Moreover, alone or in combination with the Examiner's other references Hoon does not teach the categories and selection criteria of genetic markers of the present invention. In making the impermissible allele combinations of the Office Action of 07/01/2003, the Examiner has been guided solely by the present invention, and not by Hoon or by any prior art of record. Hoon is not a patent on the idea of combining alleles for improved detection sensitivity. Rather, it is a patent issued for an apparent non-obvious combination of alleles for apparent novel and non-obvious uses. As such, if anything, Hoon stands for the patentability, not unpatentability, of the present disclosure.

Thus, the Examiner's combination of Hoon with previously cited references fails to teach every element of the presently claimed invention and, without more, the Examiner is unable to sustain a *prima facie* case of obviousness. In view of the above, the Applicant respectfully requests that the rejection be withdrawn.

2. Hoon does not provide a suggestion or motivation to combine the recited elements.

An essential requirement for a *prima facie* case of obviousness is whether a person of ordinary skill in the art would be motivated to modify the reference to arrive at the claimed invention. The Applicant asserts that the Examiner has not met the burden of

establishing a *prima facie* case of obviousness. *Prima facie* obviousness based on a combination of references requires that **the prior art** provide "a reason, suggestion, or motivation to lead an inventor to combine those references."[1] (Emphasis added.) "The range of sources available, however, **does not diminish the requirement for actual evidence**. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence"."[2] (Emphasis added). The suggestion to combine prior art references must come from the cited references, not from the applicant's disclosure.[3]

As set forth in *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000):

> "A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. . . . Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher."
>
> Most if not all inventions arise from a combination of old elements. . . . Thus, every element of a claimed invention may often be found in the prior art. . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. . . . Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." (Emphasis added).

The Examiner's rejection does not establish the requisite suggestion in the art to combine elements disclosed in the prior art. "A rejection cannot be predicated on the mere identification . . . of individual components of claimed limitations. Rather, **particular findings must be made** as to the reasons the skilled artisan, with no knowledge of the claimed invention, would have

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1 *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

2 *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

3 *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1998)

selected these components for combination in the manner claimed."[4] (Emphasis added). The need for a specific suggestion in the cited references is absolute: "The factual inquiry whether to combine references must be thorough and searching. It must be based on **objective evidence of record**. This precedent has been reinforced in myriad decisions and cannot be dispensed with."[5] (Emphasis added).

In the Office Action of 07/01/2003 the Examiner argues:

> "Moreover, given the teachings of Hoon that sampling multiple markers provides increase (sic) sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery."
> (page 9)

Contrary to legal requirement, the Examiner's conclusory and unsupported assertion is not evidence. The Examiner does not, and cannot, point to which specific teachings in Hoon motivate the ordinary artisan to combine the claimed elements thereby arriving at the genomic profiles of the present invention for use in a perioperative subject because no such teachings exist in Hoon. Rather, the Examiner's assertion reflects the absence of evidence, and thus does not fulfill the obligation of the Patent and Trademark Office.

Because the Examiner has failed to establish motivation to modify Hoon and other references of the Examiner's combinations to arrive at the claimed invention, a *prima facie* case of obviousness must fail. In view of the above, Applicant respectfully requests that the rejection be withdrawn.

3. Hoon does not provide a reasonable expectation of success

Alone or in combination with other references cited by the Examiner, Hoon does not teach "two or more nucleic acid markers in two or more genes known to be associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action." None of the Examiner's references alone, or in combination with one another, or in combination with Hoon teach,

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[4] *Ecolochem*, 227 F.3d, 1361, 1375, 56 USPQ2d 1065, 1076, quoting *Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317.

[5] *In Re Sang Su Lee*, 277 F.3d 1338, 1341, USPQ2d 1430, 1433.

suggest or motivate the ordinary artisan in how to perform the selection and detection of alleles for application in the perioperative interval. Therefore, the Examiner cannot advance any evidence in support of the contention that the artisan using the methods of Hoon would have had a reasonable expectation of success. Because the Examiner is not able to demonstrate that a reasonable expectation of success may be found in Hoon, the third prong of a *prima facie* case of obviousness is defective, as are prongs one and two.

Because not one, but each of the three elements of a *prima facie* case of obviousness is lacking, the Applicant respectfully requests that the rejection under 35 USC §103(a) for alleged obviousness be withdrawn.

E. The Examiner's Rejection is Defective as a Matter of Fact

In order to further prosecution of the present case, and while under no legal obligation to do so, the Applicant has provided ample, specific and objective evidence in the form of published references, peer reviews, a Declaration, and a Practice Advisory showing the Examiner's inability to fabricate a *prima facie* case of obviousness. Contrary to the Examiner's speculations, this evidence documents that at the time the invention was made, ordinary artisans did not, and do not, agree with the Examiner regarding the obviousness of perioperative genomic profiles. Despite the Examiner's mischaracterizations and misconstructions of this evidence, these facts remain uncontested.

1. The Anesthesia Patient Safety Foundation (APSF) Review Stands for Non-Obviousness of the Present Claims

The APSF review of a grant application entitled "Perioperative Genomic Profiles" states:

> "The APSF committee members reviewing your proposal to study genetic profiles were impressed by the elegance to the proposal. It would take the issue of patient safety **in a new direction.**"

And:

> "As anesthesia practice has moved toward determining the ratio of quality to cost, this study seems to be **going in the opposite direction**. It suggests we test everyone in the hopes we find something on almost everyone. **The direction of anesthetic evaluation is**

presently to not routinely do any preoperative studies." (Declaration of Kirk Hogan, M.D., 02/08/2002).

Thus, when presented with the subject matter of the present invention, medical practitioners would **not**, as the Examiner has improperly guessed, "have been motivated to have screened individuals to provide individualized surgery to determine the genetic composition of the individuals to provide individualized diagnosis." (Office Action 07/01/2003, page 10).

In the present Office Action the Examiner argues:

> "Regardless of whether the test is viewed as not cost effective for broad application for all patients, it remains obvious to sample individuals before surgery for known mutations which affect surgical outcomes." (Office Action 07/01/2003, page 13).

Not only is the Examiner's assertion conclusory and unsupported, but the Examiner continues to confuse the fact of the Examiner's error (which the Examiner has not refuted) with the Examiner's attempt to rationalize it. In turn, if perioperative genomic profiles are obvious, where is the Examiner's evidence? When confronted with objective, hard evidence concerning what an ordinary artisan would or would not have been motivated to do, the Examiner is distracted by cost and economic benefit analysis. In the Office Action of 07/01/2003 the Examiner quotes the APSF review that "the state of the art teaches that **such methods should not be carried out**" and that the study is "**without clear clinical value**". (Page 13). Applicant requests that the Examiner take these objective assessments of the ordinary artisan's motivation at the time the invention was made at face value.

2. Gregory Stands for Non-Obviousness of the Present Claims

Contrary to the Examiner's guesses concerning what an ordinary artisan would have recognized or been motivated to do at the time the invention was made, Gregory, in Pediatric Anesthesia, 2002, states "The present consensus, therefore, is that **routine screening tests are of little value**." and that "There is a growing movement to **omit all routine testing**." In the Office Action of 07/01/2003 the Examiner fails to confront this objective and factual evidence in refutation of the Examiner's speculations. If the Examiner's suppositions concerning an

ordinary artisan's recognition of benefits and motivation to perform genomic profiles in the perioperative interval were true, they would be found here, and they are not.

3. Kirby Stands for Non-Obviousness of the Present Claims

Similarly, in Clinical Anesthesia Practice, 2002, Kirby states"

> "There are abundant data supporting the concept that routine laboratory screening tests are not cost-effective in the asymptomatic patient." (Page 12).
>
> And:
>
> "For the apparently healthy, asymptomatic male who is <40 years of age and who is undergoing surgery with minimal expected blood loss, **no perioperative testing is necessary**." (Page 12). (Emphasis added).

To these factual and objective statements refuting the Examiner's assertions of the obviousness of the present invention, in the Office Action of 07/01/2003 the Examiner replies:

> "While routine screening has not yet reached the point of being cost effective and highly efficient, the cited art still provides a suggestion that with regard to the RYR1, BchE, prothrombin, etc. genes, testing prior to surgery would be certainly advantageous since mortality and complications may be avoided." (Page 15)

In this single statement the Examiner makes a multiplicity of errors. First, the assertion is conclusory and unsupported. Second, the Examiner is unable to point to cited art which makes the Examiner's suggestion. Third, a "certainly advantageous" standard of obviousness is not the law (vide supra). Fourth, in *In re Sang Su Lee* the Federal Circuit expressly prohibits this kind of substitution of the benefits of an invention for objective evidence of an invention's obviousness by the Patent and Trademark Office.[6] Fifth, distracted by peripheral issues of cost and efficiency, the Examiner is ignoring the objective evidence of the

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[6] *Id.*

fact that ordinary artisans did **not** and do **not** recognize the benefits, and were not motivated to practice, genomic profiling on the perioperative subject.

4. Hopkins stands for Non-Obviousness of the Present Claims

Further evidence regarding what an ordinary artisan would have recognized or been motivated to do at the time the invention was made was provided by the Applicant in Hopkins, 2000. In the Office Action of 07/01/2003 the Examiner quotes Hopkins:

> "the complexity of the molecular genetics of MH precludes DNA-based diagnosis at present. Thus, a modern analysis of the molecular genetics of MH concludes that DNA-based testing for MH is precluded and not desirable." (Pages 15-16)

Hence, the Applicant has provided to the Examiner objective evidence that the Examiner's speculations concerning the motivations of an ordinary artisan at the time the invention was made are **in clear error**. In **direct opposition** to the objective evidence of the Hopkins reference, in the 07/01/2003 Office Action the Examiner argues:

> "The ordinary artisan would have **clearly recognized the benefit** of testing an individual prior to surgery and subjection to anesthesia for known genetic markers associated with a condition which was triggered by anesthetics." (Page 9).
>
> And:
>
> "The ordinary artisan **would have been motivated to have screened individuals** to provide individualized surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Thus, the ordinary artisan **would have been motivated to test patients within two days prior to surgery** for mutations within any known genes for known mutations which are associated with known conditions for the expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure." (Page 10).

Rather than acknowledging the reference and the clear error, in the Office Action of 07/01/2003 the Examiner then makes the peculiar assertion "The Claims are not drawn to diagnosing MH." Of course, the claims are drawn to diagnosing MH (e.g., by genomic testing for predisposing alleles in the RYR1 and other MH genes) among many other conditions in the perioperative interval. In the subsequent statement the Examiner makes the still more peculiar observation "Furthermore, the reference of Hopkins provides as much enabling disclosure as the instant application." (Office Action 07/01/2003). Not only is the Examiner now inappropriately arguing §112 issues in attempting to support the *prima facie* case of obviousness, but the assertion is utterly wrong. Hopkins does not teach multiple nucleic acid genetic markers in multiple genes associated with multiple conditions to generate a genomic profile for use in selecting a perioperative treatment course of action.

5. The Second Declaration of Kirk Hogan, M.D., and the "Practice Advisory for Preanesthesia Evaluation: A Report by the American Society of Anesthesiolgoists Task Force on Preanesthesia Evaluation", Stand for the Non-Obviousness of the Present Claims

In the Office Action of 07/01/2003 the Examiner argues:

> "The declaration asserts that no perioperative genetic testing of any kind is advocated, discussed or mentioned. This silence with respect to genetic testing does not mean that the testing would be unobvious." (Page 16)

As discussed in Section I.B. supra, it is not the Applicant's duty to prove non-obviousness. Rather, the Examiner must provide objective evidence of obviousness to establish a *prima facie* case of obviousness in the first instance. To the contrary, the 2002 Practice Advisory's silence on the matter of genetic testing in the perioperative interval **directly contradicts** the Examiners assertions. For example, the Examiner argues:

> "The **ordinary artisan would have clearly recognized the benefit** of testing an individual prior to surgery and subjection to anesthesia for known genetic markers

associated with a condition which was triggered by anesthetics." (Office Action 07/01/2003, page 9).

And:

"The **ordinary artisan would have been motivated** to have screened individuals to provide individualized surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any known genes for known mutations which are associated with known conditions for the expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure." (Office Action 07/01/2003, page 10).

And:

"The **ordinary artisan would have recognized** that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise." (Office Action 07/01/2003, page 10).

And:

"... **the skilled artisan would be motivated** to screen markers which were well known at the time of the art simultaneously or in tandem for the benefits of providing the most complete amount of information possible." (Office Action 07/01/2003, page 11).

And:

"While routine screening has not yet reached the point of being cost effective and highly efficient, the **cited art still provides suggestion** that with regard to RYR1, BchE, prothrombin, etc. genes, testing prior to surgery would be certainly advantageous since mortality and complications may be avoided." (Office Action 07/01/2003, page 15).

In the Office Action of 07/01/2003, the Examiner then concedes:

"While the article (i.e, the Practice Advisory) may not specifically consider genotypes for preanesthesia evaluation **does not** provide evidence that the combination of the cited references **do not** provide the legal standard for obviousness." (Page 16). (Emphasis added.)

A flaw in the Examiner's convoluted assertion is that it is not the Applicant's responsibility to prove non-obviousness (vide supra). Rather, it is the Examiner's and Patent and Trademark Office's obligation to provide objective evidence of obviousness (that is, that the combination of cited references **do** provide the proper legal standard for obviousness), and this duty has not been met. Nor is it the responsibility of the Applicant to provide a reference that supports "the assertion that preoperative care precludes the testing of genetic markers", or that "preoperative tests should **not be done**." (Office Action 07/01/2003, page 17). To the contrary, the Practice Advisory, and all other objective evidence of record, stands in stark and simple contrast to the Examiner's lack of evidence and erroneous suppositions regarding what an ordinary artisan might have clearly recognized or been motivated to do. In other words, given the impossible task of showing that the art **had *not* thought of something** that had not yet been created, Applicant has (although not required to) provided the best surrogate evidence—evidence that tends to show that, to the extent artisans have addressed the issue (even after the filing of the present invention), there has been no motivation to move in the direction of the presently claimed invention.

F. Claims 84, 85, 92, 93, 99 and 100 are not "Routine Optimization"

In the Office Action of 07/01/2003 the Examiner argues:

"With respect to the claims drawn to specific numbers of markers, for example 5 and 10 or more mutations, the skilled artisan would be motivated to screen markers which were well known at the time of the art simultaneously or in tandem for the benefits of providing the most complete amount of information possible." (Page 11)

The Examiner's assertion is conclusory and unsupported by objective, factual evidence. Other than improperly reciting the benefits of the invention, the Examiner has provided no evidence regarding what an ordinary artisan recognized or would have been motivated to do at the time the invention was made.

The Examiner also argues:

"As noted *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization to 5 or more mutations is not considered inventive and no evidence has been presented that the marker selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art." (Office Action 07/01/2003, page 11)

In this assertion the Examiner makes a number of erroneous arguments. First, the general conditions of claims 84, 85, 92, 93, 99 and 100, that is, the independent claims upon which they are based, are **not** disclosed in the prior art. Second, marker selection and marker number guided by the marker categories and selection criteria of the Specification are not "routine optimization" or "routine experimentation" or "workable ranges". Third, it is not the Applicant's burden to provide evidence that the marker selection is "other than routine". To the contrary, the Examiner must first provide objective evidence that marker selection is routine, and this the Examiner cannot do other than to reiterate conclusory and unsupported guesses. Fourth, the Examiner does not specify what the Examiner considers to be the closest prior art for 5 or more, or 10 or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action.

G. The Examiner Rebuffs the Applicant's Request for Objective Evidence

In the preceding Amendment and Response to Final Office Action the Applicant notes that "the examiner's burden has not been met with clear and convincing evidence in the form of "anything other than the Examiner's conclusory guesses.", and that "the examiner cannot rely on gut feelings or personal beliefs no matter how strongly the Examiner holds these convictions." (Office Action 07/01/2003, page 12). In the present Office Action the Examiner responds:

> "The arguments of counsel cannot take the place of evidence in the record. In re Schultze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration included statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of reference, and allegations that the author(s) of prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the inoperability of the prior art must be supported by evidence, not argument." (Page 12)

To the contrary, the Applicant's requests that the Examiner abide by duties established by statute, the MPEP and case law to provide objective evidence in support of a *prima facie* case of obviousness are not "arguments of counsel" or ""attorney statements". Applicant need provide no facts to require the Examiner to meet a **legal** obligation. Rather, Applicant asks for this evidence and the Examiner is mute. The Examiner has utterly failed to address Applicant's response that the law calls for the Examiner to provide factual evidence.

The Examiner also argues:

> "The ordinary artisan would have had a reasonable expectation of success for assaying for genetic markers prior to surgery." (Office Action 07/01/2003, page 13)

Again, Applicant requests the Examiner to provide evidence to sustain the assertions. In its absence the Examiner's conjecture is conclusory and unsupported.

H. Quane Does Not Void Non-obviousness

The Examiner argues:

> "The response does not specifically address Quane who explicitly teaches that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided." This statement provides motivation to the ordinary artisan to sample prior to treatment with anesthetics which trigger MH." (Office Action 07/01/2003, page 16).

Quane fails to teach that samples are tested in the perioperative period. The Examiner points to language on page 141, column 2 of Quane where the reference states "Once an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided." However, this language does not teach testing in the perioperative period as claimed. In Quane, subjects were tested following a poor reaction to an anesthetic during surgery. These **post-surgical** subjects were tested to identify a polymorphism. In contrast to the presently claimed invention, these subjects were not tested in the perioperative period as claimed, nor would these patients be tested in the perioperative period as claimed for any future surgery as they have already been characterized. Therefore, there is no teaching in Quane to conduct perioperative testing as claimed. Quane does not teach or suggest that anyone (e.g., people who are generally believed to be healthy going into the test) should be screened prior to surgery.

Moreover, the Quane reference only relates to a single condition or phenotype, i.e., MH. Alone, or in combination with the Examiner's other references, Quane does not teach two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile for us in selecting a perioperative course of action.

In order to further the prosecution of the present case, while not acquiescing to the Examiner's arguments and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended cancelled claim 42, and added claim 74, reciting "associated with two or more conditions". In order to further the prosecution of the present case, while not acquiescing to the Examiner's arguments and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended cancelled claims 62, 69 and 70, and added claims 94, 101 and 102, reciting "said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure;". In order to further the prosecution of the present case, while not acquiescing to the Examiner's arguments and retaining the right to prosecute the original claims (or

similar claims) in the future, Applicant has amended cancelled claim 70, and added claim 102, reciting "adverse responses".

For the foregoing reasons, Applicant submits that the Examiner's rejection of cancelled claims 42-73, and added claims 74-105, was erroneous, and reversal of the rejection is respectfully requested.

II. CLAIM 55, AND ADDED CLAIM 87, ARE NON-OBVIOUS

Claim 55 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bidwell (Technique, Vol.2, pages 93-100, 1990) (hereinafter referred to as Bidwell). (Office Action 07/01/2003, page 2). Applicant respectfully disagrees.

A *prima facie* case of obviousness requires the Examiner to cite to a reference which a) discloses all the elements of the claimed invention, b) suggests or motivates one of ordinary skill in the art to combine the claim elements to yield the claimed invention, and c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements negates a finding of a *prima facie* case and, without more, entitles the Applicants to allowance of the claims in issue. (MPEP) The Examiner argues that cancelled claim 55 and added claim 87 (corresponding to previous claim 55), would have been obvious to one of ordinary skill in the art. To the contrary, the Examiner has failed to establish not one, but all three of the requirements for a *prima facie* case of obviousness, thus entitling Applicant to withdrawal of this rejection.

A. Bidwell does not teach all elements of the claimed invention.

For the Examiner to establish the *prima facie* case of obviousness all claim limitations must be taught or suggested by the prior art. To the contrary, the Examiner's cited reference (i.e., Bidwell) teaches a genotyping method ("PCR fingerprinting"), for detection of single exon polymorphisms (No. 2), in a single gene (HLA-DRB), for a single condition (allotype matching).

1. Bidwell does not teach a "perioperative subject".

The Examiner argues:

"If the allotyping of Bidwell is performed prior to surgery, as required by the claims, and it is determined that the transplant is not an appropriate match, then the surgery can be aborted and the risk for complications eliminated. Therefore, there would be no risk for complications during said surgical procedure because **there would not be a surgical procedure**." (Office Action 07/01/2003, page 3). (Emphasis added.)

The Examiner concedes, "Bidwell does not specifically teach performing a transplant upon finding a match of HLA-DR/Dw allotypes." (Office Action 07/01/2003), page 3). However, cancelled claim 55, and added claim 87, explicitly recite the element "**subjecting said subject to a surgical procedure**." Hence, the Examiner explicitly acknowledges that Bidwell is missing a key element of the claims. On this basis alone, the rejection must be withdrawn.

In order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended cancelled claim 55, and added claim 87, to recite "providing a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure;". The Examiner further admits that this element is not taught by Bidwell.

In view of the above, Applicant respectfully requests that the rejection be withdrawn.

2. Bidwell does not teach "perioperative phenotypes"

The Examiner argues: "Therefore, the claims which require selecting conditions, i.e. transplant matches, by assaying two or more nucleic acid genetic markers in two or more genes, prior to a surgical procedure would have been obvious to the ordinary artisan at the time the invention was made." (Office Action 07/01/2003, page 4). The Examiner is in error, and has misread the claim. Cancelled claim 55, and added claim 87, recite "subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes **known to be associated with perioperative phenotypes** to generate a genomic profile" Hence, the claims explicitly teach a plurality of **phenotypes**. (Emphasis added). To the contrary, Bidwell teaches only a **single** phenotype i.e. HLA-DRB allotyping. As the Examiner concedes, Bidwell does not teach detection of two or more nucleic acid markers in two or more genes associated with more than a single condition:

> "None of the cited references (i.e., including Bidwell) specifically discuss testing multiple known markers which are associated with different conditions, i.e. known genetic markers into a single assay for determining whether individuals are at risk during surgical procedures." (Office Action 10/18/2002, page 21).

Indeed, each of the elements of generating a genomic profile by detecting multiple nucleic acid markers in multiple genes associated with multiple conditions in a perioperative subject once a surgical procedure has been scheduled are missing from Bidwell.

In order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended cancelled claim 55, and added claim 87, reciting "subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes known to be associated with two or more perioperative phenotypes to generate a genomic profile."

In view of the above, Applicant respectfully requests that the rejection be withdrawn.

3. Bidwell does not teach the claimed genomic profiles

Contrary to the cancelled claims 55-59, and added claims 87-91, Bidwell does not teach genetic markers associated with a pharmacological response. Bidwell does not teach genetic markers associated with a pharmacological response, wherein the pharmacological response is to an anesthetic. Bidwell does not teach genetic markers associated with a pharmacological response wherein the pharmacological response is to drugs used in anesthetic practice. Bidwell does not teach two or more nucleic genetic acid markers comprising a mutation in two or more genes selected from the group *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2*. Guided by Bidwell an artisan of ordinary skill could not protect the patient in the perioperative interval from complications and conditions arising from genetic variations in these and other genes taught by the present invention. Bidwell does not teach multiple suitable genotyping methods disclosed in the Specification (pages 34-45). Bidwell does not teach criteria for selection of perioperative markers. (Specification, pages 27-29). Bidwell does not teach categories of perioperative markers. (Specification, pages 29-30). Bidwell does not teach applications and interventions of specific perioperative markers. (Specification, pages 30-34).

Thus, Bidwell fails to teach every element of the presently claimed invention and fails to teach reasons for moving in the direction of the present invention and, without more, the Examiner is unable to sustain a *prima facie* case of obviousness.

In view of the above, Applicant respectfully requests that the rejection be withdrawn.

B. Bidwell does not provide a motivation to combine the recited elements.

An essential requirement for a *prima facie* case of obviousness is whether a person of ordinary skill in the art would be motivated to modify the reference to arrive at the claimed invention. Bidwell does not teach or suggest how to select and detect nucleic acid markers and associated perioperative phenotypes to generate a perioperative genomic profile. Bidwell cannot provide such a motivation because it does not teach the recited elements of the present invention (see II.A.3., above). One skilled in the art and aware only of Bidwell but not the present invention, could not have been motivated to perform the modification by the Bidwell reference. Bidwell does not suggest that alleles in genes encoding, for example, *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2* be combined into a perioperative genomic profile. Because the Examiner has failed to establish motivation to modify Bidwell to arrive at the claimed invention, a *prima facie* case of obviousness must fail.

In view of the above, Applicant respectfully requests that the rejection be withdrawn.

C. Bidwell does not provide a reasonable expectation of success

Bidwell does not teach "two or more nucleic acid markers in two or more genes known to be associated with two or more perioperative phenotypes." To the contrary, Bidwell teaches testing for a **single** condition (allotype matching), for polymorphisms in a **single** exon (No. 2), in a **single** gene (HLA-DRB). To this end Bidwell teaches three PCR primers (i.e., PL8/12, GH46, GH50) and separation of the resultant PCR products by nondenaturing gel electrophoresis. Hence, the method taught by Bidwell could not possibly work in the present invention. The multiple nucleic acid markers and genes of the present invention are sufficiently unrelated in structure such that Bidwell's two primer pairs (i.e., GH46 and GH50, PL8/12 and GH50) offer no hope of success to the ordinary artisan in generating the perioperative genomic profiles of the instant claims. The Examiner cannot advance any evidence in support of the contention that the artisan using the methods of Bidwell would have had a reasonable expectation of success.

Because the Examiner is not able to demonstrate that a reasonable expectation of success may be found in Bidwell, the third prong of a *prima facie* case of obviousness is defective, as are prongs one and two.

Because not one, but each of the three elements of a *prima facie* case of obviousness is lacking, the Applicant respectfully requests that the rejection of cancelled claim 55, and added claim 87, under 35 USC §103(a) for alleged obviousness be withdrawn.

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